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TAU-PET IMAGING OF BRAIN DAMAGE IN HEAD INJURY

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ABSTRACT: Positron emission tomography (PET) imaging has been broadly used in the study of brain damage for a long time. However, PET has been mostly used for the assessment and detection of neural activity after brain damage. Tau proteins play a significant role in a variety of degenerative neurological conditions. Post-mortem neuropathology studies of victims of repeated and severe head trauma have defined a unique spatial expression of neurological tauopathies in these individuals known as chronic traumatic encephalopathy (CTE). The current review assesses the role of tau in head injury, the state of tau radiotracer development, and the potential clinical value of tau-PET derived from head injury studies. There are variations in the binding patterns between different tau radiotracers. Therefore, the present work is commenced with a general review of TBI and CTE, followed by the chronic and acute pathophysiological consequences of TBI. In the following, beta-amyloid, glycolysis, and tau protein radiotracers are assessed critically, considering the most recent and available imaging studies. Considering the scientific relevance of these radiotracers to the molecular processes concerning Traumatic brain injury (TBI) and CTE and the inclusive evidence of radiotracer selectivity and specificity, this work will measure the positive and negative factors of every radiotracer. Nevertheless, there is consistent uptake in certain regions of the brain that has been observed across different studies. However, aberrant binding is expected given the variation in small studies and potential off-site radiotracer binding.

INTRODUCTION:

Neuropathology of Tau Proteins in Head Injury: Tau protein expression is concentrated in the central nervous system (CNS) [1]. Tau in the human brain is mostly contained in neurons, though minor expressions have been observed in astrocytes and oligodendrocytes [2]. Tau proteins in intraneuronal regions are concentrated within axons and a minimal prevalence has been observed in somatodendritic regions, including the cellular membrane, nuclear membrane and mitochondrial membrane [1, 3]. While multiple functions of tau proteins have been characterized, the most common ones are involved in stabilizing microtubule (MT) structures, membrane binding, and axonal transport [4].

Recent findings have also suggested that the interactions between MT and tau proteins are proposed to allow long labile domains to allow for dynamic growth and contractions [5]. Nevertheless, the functions of tau are varied depending on the location of tau proteins. In cytoskeletal regions, the binding of tau proteins to MT, acts either to directly

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stabilize MT or to create a bridge to link MT and other cytoskeletal structures. Tau proteins are necessary for proper formation of terminals, post-synaptic structures, and dendritic spines where tau proteins act as neurotrophic factors in neurogenesis [6].

Certain domains of tau protein have the capability of binding to the lipid bilayers in the cellular membrane, and while the purpose of such membrane associations is speculated, the prevalence of tau-membrane binding is correlated with tau aggregation. Tau proteins exhibit similar binding processes, and the most characterized binding interactions have been those involving MT. Tau proteins are natively unfolded. A paperclip form of tau is found in the intracellular space as a result of intramolecular binding; otherwise, binding interactions with the MT structure alter the protein to expose the MT binding region of the tau proteins, which allows interactions between MT structures and the tau protein **Fig. 1**.

Tau proteins exist in eight different conformations, and six isoforms are derived from alternative splicing of the MT-associated protein tau (MAPT) gene[7]. The six isoforms are differentiated by the number of MT binding repeats and the number of N-terminal inserts (0N, 1N, 2N) in the C-terminal (3R, 4R). The ratio of isoforms varies over the developmental period as well as between regions of the human brain. For instance, the fetal brain only expresses one form of the tau isoform, while a fully developed brain confers all six isoforms. The 3R and 4R isoforms are equally expressed in the cerebral cortex of healthy adults [8]; otherwise, there will be a notable discrepancy in the prevalence of N-terminal variants. For example, 0N, 1N, and 2N tau represent 40, 50, and 10% of the total CNS tau, respectively [9]. There are significant differences between humans and other species concerning the proportions of tau protein isoform. Once synthesized, tau proteins may undergo a variety of post-translational modifications, including phosphory-lation, glycation, acetylation, oxidation, poly-amination, sumoylation, and ubiquitylation. Tau proteins are salient for understanding head injuries. Depending on their severity, head injuries can produce a series of complex and diverse neurophysiological consequences. A primary injury includes the immediate consequences of the physical insult, while secondary injury relates to a pathophysiological cascade. A common category of primary injuries is diffuse axonal injuries (DAI), which result from torsion and blunt force. Specifically, external forces can harm the integrity of axonal structures such that axonal MT structures release previously bounded tau proteins into the parenchymal cerebrospinal fluid (CSF). Secondary injury has been associated with inflammatory pathways activation, neuronal metabolism and perfusion alteration, excitotoxicity, free radical generation, mitochondrial dysfunction, axonal degeneration, and neuronal dysfunction [10]. This should be noted that secondary injury (*e.g.,* axonal degeneration) has been understood as being the most contributory to the proliferation of tau proteins in the parenchymal space. This relationship between free tau proteins as a result of head trauma has been investigated by many studies in the context of fluid biomarkers. Following traumatic brain injuries (TBI), biomarkers can be mainly assayed in peripheral blood or CSF, though CSF is often preferred [11].

Several studies have thoroughly confirmed the association of several CSF biomarkers with axonal injury after mild TBI (mTBI), moderate TBI, and severe TBI (sTBI). More sensitive assays utilized by studies on sports-related mTBIs are associated with acute increases of tau in plasma, where the concentration of tau correlated to the duration of post-concussive symptoms and the concentrations steadily declined during rehabilitation [12]. STBI events are correlated with greater concentrations of tau in CSF samples, where tau protein levels in ventricular CSF are directly related to TBI severity, lesion size, hypoxia, and clinical outcomes [13].

In individuals with repeated injury (*e.g.,* boxers and contact sport athletes), elevated levels of tau in CSF samples have been observed more than a week after the sporting event, where normalization of tau levels occurred two to three months from the incident. Within the context of head injury, the most serious consequences of the accumulation of tau proteins are seen in unique neurological tauo-pathies, namely chronic traumatic encephalopathy (CTE), where tau aggregation is linked to subsequent neurodegenerative processes [14]. Epidemiological studies have linked single and repeated events of TBI to the development of

tauopathies. While the etiology of tauopathies is somewhat speculative, the pathological characterization of neurological tauopathies is generally agreed upon [15]. Tauopathies are defined by the intraneuronal presence of tau aggregates, termed neurofibrillary tangles (NFT), which are composed of multiple units of hyperphosphorylated MT-associated tau isoforms. This form of neurodegeneration leads to a unique distribution and identity of prions. In most tauopathy cases, tau proteins are hyperphosphorylated to become unbounded from MT structures. These hyperphosphorylated proteins then accumulate within cells with MAPT mutations. However, changes in isoforms or phosphorylation patterns as a result of such mutations result in tau aggregation that is insoluble and harmful to neuronal function and axonal transport [16]. Tau aggregates retain prion properties by way of seeding and spreading [17]. Minimal exposure to tau seeds can further lead to misfolding and aggregation. This phenomenon is observed when tau proteins are mislocalized into the soma and dendrites are transferred between the neurons. It has been observed that tau proteins can spread using the connectome network pattern and either spread pre-formed NFT or seed subsequent tau accumulation. Sparse tau aggregation generally and naturally develops with age. However, an increased density and unique distribution of tau and other abnormal protein aggregates (*e.g.,* beta-amyloid plaques) in the context of clinical dementia become indicative of neurodegenerative disease. Concerning TBI, NFTs can be observed within six hours of the event, and post-mortem studies of those with single-event moderate to severe TBIs have shown higher levels of NFTs in comparison with controls. It is further understood that the risk of CTE is directly related to the number and severity of TBI events.

Interestingly, while the distribution of tau aggregates and, to a lesser extent, beta-amyloid plaques is unique in CTE, there is not unique phosphorylation or a specific isoform that differentiates CTE from other neurodegenerative conditions [18]. Further, the ratio of tau proteins to beta-amyloid plaques is particularly elevated in CTE and is a unique characteristic of this neurodegenerative condition.

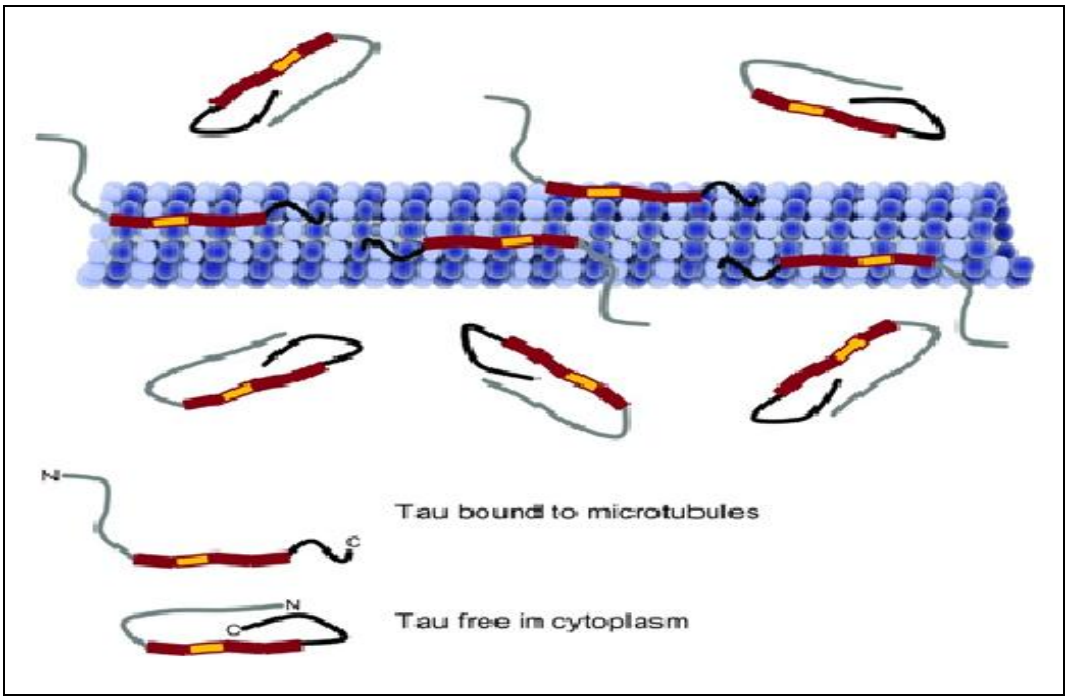

FIG. 1: TAU BINDING TO MICROTUBULES. AS DEMONSTRATED, TAU IS LINKED TO MICROTUBULES, MAINLY BY THE MICROTUBULE-BINDING DOMAIN, WHICH IS COMPRISED OF THREE OR MAYBE FOUR REPEATS. TERMINI N AND C OF TAU ARE FIRMLY ASSOCIATED WHEN TAU WITHIN THE CYTOPLASM IS FREE, WHICH ENCOURAGES THE SUGGESTED "PAPER-CLIP" MODEL OF TAU CONFORMATION. REGARDING BINDING TO MICROTUBULES, THE N TERMINUS OF TAU EXTENDS FORWARD FROM THE SURFACE OF THE MICROTUBULE AFTER THE SEPARATION OF THE TERMINAL REGIONS OF TAU. THIS IMAGE WAS USED HAVING PERMISSION FROM GUO *et al.*

Tau Radiotracers in Head Injury: The strong link between the presence of NFT and neuro-cognitive decline has strongly motivated the development of tau radiotracers that can assess the magnitude and location of abnormal protein aggregates [7]. In the context of most tauopathies, tau radiotracers are required to cross plasma cell membranes and the blood-brain barrier to reach intracellular tau proteins. Tau NFT radiotracers must provide high selectivity given the similar structure of NFT and β-amyloid aggregates. Furthermore, radiotracers must account for the variation in NFT with respect to tertiary structures, post-translational modifications, and isoforms. As such, there is a need for specificity and breadth when developing tau radiotracers.

Interestingly, these challenges are not considered significant in the application of tau imaging in the context of head injury. Limitations in the concentration of tau proteins compared to beta-amyloid plaques have posed a significant challenge to tau imaging in dementias, but this is not the case in CTE, in which the prevalence of tau is significantly greater than that of beta-amyloid. In that capacity, highly specific tau radiotracers can excel in binding to tau aggregates with less risk of off-site binding. Additionally, there are higher concentrations of tau aggregates in perivascular space[19, 20], which allow easier access of radiotracers to tau aggregates. As a result, tau radiotracers are likely to perform well in the context of CTE, compared to other tauopathy dementias.

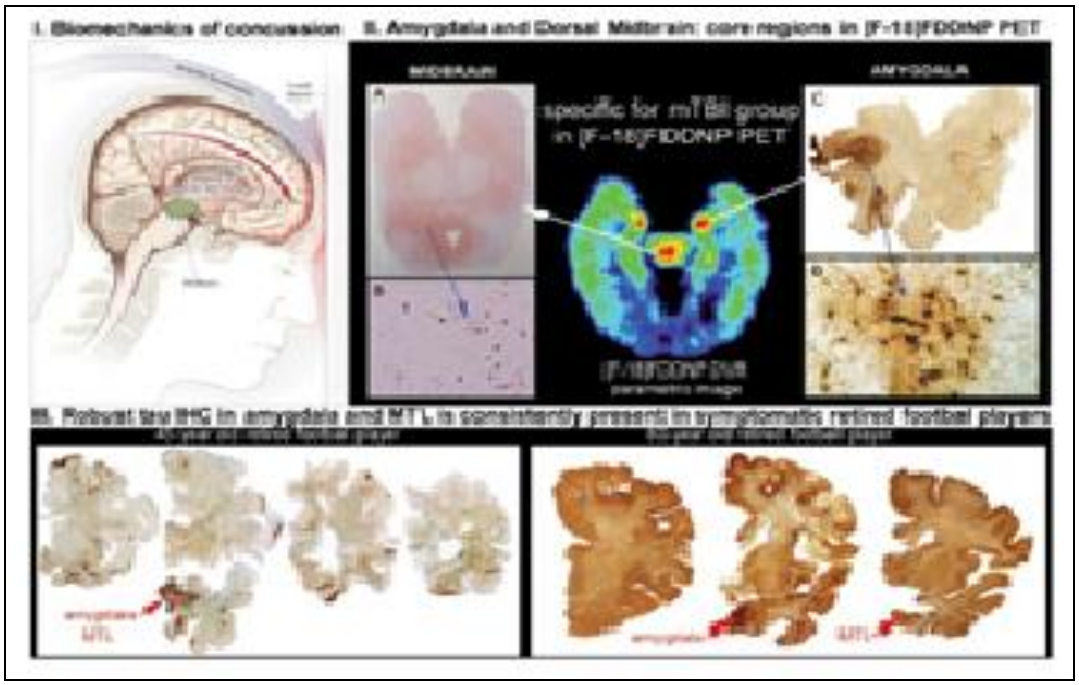

FIG 2: BOTH THE MECHANISTIC CONCEPT OF INJURY (I) AND THE RESULTS OF NEUROPATHOLOGICAL EXAMINATIONS IN DECEASED RETIRED NFL PLAYERS WITH PREMORTEM COMPLAINTS OF FUNCTIONAL IMPAIRMENTS (II AND III) SUPPORT THE ASSOCIATION OF MIDBRAIN AREAS AND AMYGDALA IN CONCUSSION-BASED MTBIS. (I) BRAIN'S ROTATION IN THE SAGITTAL PLANE IN CONCUSSIONS, JOINED BY CONSIDERABLE DECELERATIONS AND ACCELERATIONS, WILL HAVE AN OUTSTANDING NEGATIVE EFFECT ON THE BRAIN TISSUE IN THE THALAMUS (THE GREEN SHADED AREA) AND MIDBRAIN, AS WELL AS THE AFFECTED CORTICAL AREAS (THE RED AREA). IT IS HYPOTHESIZED THAT SHEARING, COMPRESSION, AND STRETCHING OF AXONS DURING THESE SUDDEN MOVEMENTS OF THE BRAIN ARE THE REASON BEHIND AXONAL INJURY. IN THE SAME MANNER, IT HAS BEEN DEMONSTRATED THAT ROTATION IN THE CORONAL PLANE LEADS TO CONSISTENT DAMAGE TO THE TRACTS IN THE MIDBRAIN REGION [27]. (II) THE RESULTS OF TAU IMMUNOHISTOCHEMISTRY ARE SHOWN IN A–D, AND THEY DEMONSTRATE THAT IN THE MTBI GROUP, AREAS OF INCREASED [18F]FDDNP SIGNAL IN AMYGDALA AND DORSAL MIDBRAIN COINCIDE WITH THE PRESENCE OF DENSE TAU DEPOSITS IN PERIAQUEDUCTAL GRAY (PAG) IN DORSAL MIDBRAIN (A AND B) AND AMYGDALA (C AND D). (III) BOTH THE MTL AND AMYGDALA AREAS ARE AFFECTED IN THE BRAINS OF RETIRED PROFESSIONAL NFL PLAYERS WHO DIED AFTER SUICIDE (LEFT; 45-YEAR-OLD RETIRED PLAYER) OR BECAUSE OF NATURAL CAUSES [RIGHT; 80-YEAR-OLD RETIRED AMERICAN FOOTBALL PLAYER]. THE FIRST AREAS HAVING A HIGH DENSITY OF TAU DEPOSITS IN THE NEOCORTEX ARE MTL AND AMYGDALA AREAS, AND THEY REMAIN AS ONE OF THE HIGHLY AFFECTED CORTICAL REGIONS AMONG MOST OF THE RETIRED NFL PLAYERS. IMAGES WERE REPRODUCED WITH PERMISSION [28].

Tau PET Imaging Studies in Head Injury: Using many of the mentioned radiotracers, many studies have applied tau PET to TBI populations. Most tau-PET imaging of individuals with single event TBIs takes place long after the original insult, while most studies include patients with years of mTBI experiences from sports or military combat. Takahata *et al.,* used [11C] PBB3-PET to assess tau patterns in 27 individuals with either repeated mTBI or sTBI in comparison with 15 healthy control subjects [21]. Increased uptake in the cerebrum and white matter correlated to psychosis and other neuropsychiatric symptoms. Gorgraptis *et al.,* applied [18F]AV145-PET in 21 subjects suffering from moderate and severe TBIs as well as 11 control (healthy) subjects. Elevated whole brain and right occipital lobe uptakes of [18F] AV145 were observed in the TBI group of that study [22]. Robinson *et al.,* observed increased white matter uptake of 18F-AV145 and notable uptakes in the cerebellum, occipital lobe, inferior temporal lobe, and frontal lobe across 16 military veterans with a history of blast neurotrauma. However, no controls were used in this study as comparators [23]. Several studies have used National Football League players as their study population, where most studies have aligned well with non-NFL populations with a few notable exceptions. Dickstein *et al.,* examined one player with [18F]AV145-PET and found increased uptake in the gray-white matter junction along with the bilateral cingulate, temporal lobes, occipital lobe, and orbitofrontal cortices [24]. Mitsis *et al.,* observed increased [18F]AV1451 uptake in one NFL player and one sTBI patient where different uptake patterns were observed. The NFL subject demonstrated higher uptake in the nigral and striatal regions, while the subcortical and hippocampal regions were more vivid in the sTBI subject's scans [25].

Okonkwo *et al.,* also observed elevated [18F]AV1451 uptake in two TBI patients in comparison with age-sex matched controls [26]. Wooten *et al.,* assessed [18F]AV1451-PET scans of five athletes, two veterans, and one vehicular accident patient compared to 11 healthy subjects, and regions with higher uptake in the TBI group were correlated with poor white matter function [27]. Larger studies, including NFL players, have been performed by Barrio *et al.,* and Stern *et al.,* in which [18F]AV1451 was applied to 16 NFL players and 31 healthy controls to find elevated uptake in the left parietal, bilateral medial temporal, and bilateral superior frontal regions. Barrio used [18F]FDDNP-PET to study uptake patterns among 14 NFL players and 28 healthy controls [28] **Fig. 2**. Although [18F]FDDNP is bound to beta-amyloid and tau aggregates, the limited prevalence of beta-amyloid in CTE implies that much of the unique uptake in these populations in comparison with the control group is likely driven by tau aggregate accumulation and not beta-amyloid deposition [28].

Nevertheless, Barrio *et al.,* noted increased uptakes in the frontal cortex, anterior cingulate gyrus, and amygdala in the NFL players **Fig. 3**. In another study, Chen *et al.,* used [18F] FDDN-PET in a study population of seven military veterans, 15 retired players with mTBI history, and 28 healthy controls. Their findings were consistent with Barrio *et al.,* but it was revealed that military personnel had limited uptake in the amygdala and striatum compared to the player population [29]. Vasilevskaya *et al.,* applied [18F] AV1451-PET to 38 former contact sport athletes [30].

In this study, the presence of APOE4 alleles aligned with high cortical gray matter PET tau uptake, such that the presence of APOE4 may incline individuals to accumulate tau aggregates more than others. Given that the present diagnosis of CTE is contingent upon post-mortem neuro-pathological examination, some of the most convincing tau-PET studies have attempted to confirm their imaging with post-mortem analysis of the brain. Mantyh et al. studied one former NFL player with [18F]AV1451-PET plus subsequent post-mortem analysis of that individual who was then diagnosed with stage III Braak NFT, TDP 43 encephalopathy, and stage IV CTE [31]. Uptake was most prevalent in degenerated and hypometabolic regions in the frontotemporal region. This was concurrent with post-mortem tau aggregates in the inferior temporal gyri, left fusiform, and juxtacortical frontal white matter. Excessive uptake with minimal tau deposition was observed in calcarine cortex, motor cortex, basal ganglia, and thalamus. Omalu *et al.* assessed the [18F]FDDNP-PET scan of one former NFL player and respective post-mortem analysis and found that [18F]FDDNP-PET uptake correlated with tau deposition, most notably in the paraventricular and parasagittal

regions of the brain as well as the brain stem [32]. No correlation was observed with TDP-43 or amyloid deposition, since those regions of the brain are mostly involved in shearing, and rotational forces were mostly linked to tau deposition; such deposition patterns would align with the unique patterns found in CTE.

Marquie *et al.,* did not perform any *in-vivo* imaging. Instead, auto-radiographic binding patterns of [18F] AV1451 were observed in five post-mortem brains diagnosed with stage II through IV CTE. [18F]AV1451 binding was observed in all NFT regions as confirmed by immunostaining, and a limited signal was observed in white matter and other non-tangle containing regions [33].

There was a correlation between the Quantification of tau burden and tracer uptake. Previously mentioned *in-vivo* studies have not found such consistent binding patterns and strong correlations, which may be indicative of a difference between the *ex-vivo* and *in-vivo* environments.

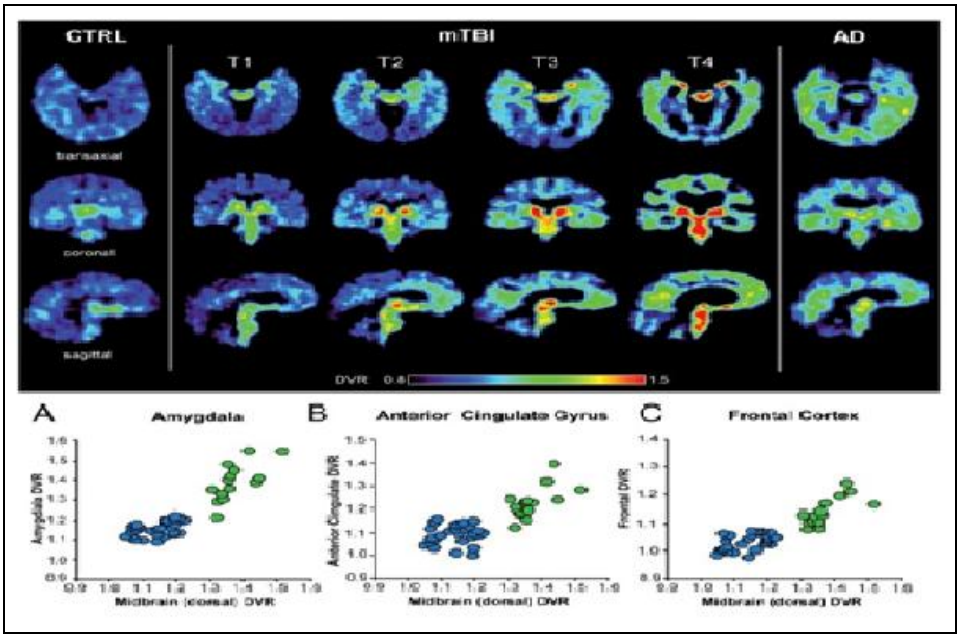

FIG. 3: (UPPER) PARAMETRIC IMAGES OF [18F]FDDNP DISTRIBUTION VOLUME RATIOS (DVR) THAT SHOW PATTERNS T1 TO T4 OF INTENSIFIED [18F]FDDNP UPTAKE THAT ARE CLEARLY SEEN IN THE MTBI GROUP IN COMPARISON TO THE COGNITIVE CONTROL SUBJECTS (LEFT). THE INVOLVEMENT OF TWO CORE AREAS, WHICH HAVE STEADILY INTENSIFIED [18F]FDDNP UPTAKE IN ALL THE FOUR PATTERNS, IS SHOWN BY THE T1 PATTERN: DORSAL MIDBRAIN (SUBCORTICAL) AND AMYGDALA (LIMBIC). THE INCREASE IN [18F]FDDNP UPTAKE IN THE ABOVE-MENTIONED TWO CORE REGIONS AND THE PROGRESSIVELY GREATER NUMBER OF CORTICAL, LIMBIC, AND SUBCORTICAL AREAS MARK T2 TO T4 PATTERNS. DESPITE THE OVERLAP OF MORE COMPLEX PATTERNS (E.G., T4) WITH AD IN THE AMYGDALA, MIDBRAIN, AND CORTEX, SIGNALS ARE ELEVATED ABOVE THE OBSERVED LEVELS IN AD (TABLE 2). FOR COMPARISON PURPOSES, AN AD CASE IS INCLUDED IN THE RIGHT-HAND COLUMN. (LOWER)A IS A 2D SCATTER PLOT DEMONSTRATING [18F]FDDNP DVR VALUES IN THE TWO CORE AREAS THAT ARE FREQUENTLY INVOLVED IN CTE (LIMBIC STRUCTURES (AMYGDALA) AND SUBCORTICAL STRUCTURES (DORSAL MIDBRAIN)), DISTINCTLY SHOWING THE SEPARATION OF MTBI AND CONTROL GROUPS. B AND C ARE SHOWING SIMILAR SEPARATION EFFECTS WHEN DORSAL MIDBRAIN IS COMPARED TO CORTICAL AREAS USUALLY RELATED TO CTE AND ITS MOOD DISORDERS; TO BE SPECIFIC, ANTERIOR CINGULATE GYRUS (ACG) (B) AND FRONTAL LOBE (C). GREEN CIRCLES INDICATE MTBI SUBJECTS AND BLUE CIRCLES INDICATE CONTROL SUBJECTS. IMAGES WERE REPRODUCED WITH PERMISSION[28]

CONCLUSION: In reviewing the literature, there are several apparent takeaways. There are variations in the binding patterns between different tau radiotracers. Nevertheless, there is consistent uptake in certain regions across studies. Moreover, aberrant binding is expected given the variation in small studies and potential off-site radiotracer bindings. However, the literature suggests that larger studies may be more consistent in finding uptake in regions where tau aggregates are normally observed in CTE populations. Overall, the evidence suggests that tau-PET imaging will continue to have a prominent role in both CTE and TBI. These studies have provided considerable

promise in imaging tau, and prospective larger studies may substantiate the use of a particular radiotracer in the assessment of long-term TBI ramifications and diagnosis of CTE. There is a notable need for future studies that incorporate *in-vivo* imaging and post-mortem pathological studies.

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